AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0019] with the following:

[0019] Figure 3 is a line graph depicting the radiolabeling formation kinetics of ~~^{177}Lu DOTA-Herceptin™~~ ^{177}Lu DOTA-HERCEPTIN™ radioimmunoconjugates.

Please replace paragraph [0020] with the following:

[0020] Figure 4 is a line graph depicting the *in vitro* serum stability as measured by instant thin layer chromatography (ITLC) of ~~^{177}Lu DOTA-Herceptin™~~ ^{177}Lu DOTA-HERCEPTIN radioimmunoconjugates.

Please replace paragraph [0021] with the following:

[0021] Figure 5 is a line graph depicting the *in vitro* serum stability as measured by size exclusion high performance liquid chromatography (SE-HPLC) of ~~^{177}Lu DOTA-Herceptin™~~ ^{177}Lu DOTA-HERCEPTIN radioimmunoconjugates.

Please replace paragraph [0022] with the following:

[0022] Figure 6 is a bar graph illustrating the comparison of the uptake in bone of ~~Herceptin™~~ HERCEPTIN immunoconjugates radiolabeled with ^{177}Lu.

Please replace paragraph [0115] with the following:

[0115] This example demonstrates the conjugation of ~~Herceptin™~~ HERCEPTIN with C-DOTA, PA-DOTA, 1B4M-DOTA (**7**), and CHX-DOTA (**14**).

Please replace paragraph [0116] with the following:

[0116] The ~~Herceptin™~~ HERCEPTIN was generously provided by Dr. R. Altemus (Radiation Oncology Branch, NCI). The ~~Herceptin™~~ HERCEPTIN was concentrated to 5 mg/mL and conjugated with either 2-(*p*-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (C-DOTA), 1,4,7,10-tetraaza-N-(1-carboxy-3-(4-nitrophenyl)propyl)-N',N'',N'''-tris(acetic acid) cyclododecane (PA-DOTA), 1B4M-DOTA (**7**), or CHX-DOTA (**14**), employing the linkage methods for aryl isothiocyanato groups that have been well described in the literature (see, for example, Mirzadeh et al.,

Bioconjugate Chem. 1, 59-65 (1990)). Unreacted or "free" ligand was separated from the conjugated antibody by dialysis in 0.15 M NH_4OAc. The average number of chelates per antibody for the conjugation products was about 1 chelate per protein moiety, as determined by the appropriate spectrometric method for these chelating agents (Dadachova et al., *Nucl. Med. Biol.* 26, 977-982 (1999); Pippin et al., *Bioconjugate Chem.* 3, 342-345 (1992)). Protein concentration was determined using the Lowry method with a standard of bovine serum albumin (Lowry et al., *J. Biol. Chem.*, 193, 265-275 (1951)).

Please replace paragraph [0117] with the following:

[0117] This example demonstrates radiolabeling and comparative radiolabeling of the C-DOTA-, PA-DOTA-, 1B4M-DOTA (**7**)-, and ~~CHX-DOTA (**14**)-Herceptin™~~ CHX-DOTA (**14**)-HERCEPTIN immunoconjugates prepared in Example 15.

Please replace paragraph [0118] with the following:

[0118] Radiolabeling with ^{177}Lu of the four immunoconjugates was performed analogously to previous reports (see, for example, Ruegg et al., *Cancer Res.* 50, 4221-4226 (1990)). The ^{177}Lu (1-3 mCi in 10-20 μL 0.1 M HCl) (U. Missouri, Columbia) was added to about 200 μL 0.15 M NH_4Ac buffer (pH 5.0-5.5) containing 300-400 μg of each of the ~~DOTA-Herceptin™~~ DOTA-HERCEPTIN immunoconjugates prepared in Example 15. The reaction mixtures were incubated at 37 °C for 1-2.5 h. The reaction kinetics were followed by taking aliquots at different times and analyzing the components using ITLC developed in 10 mM EDTA/0.15 M NH_4OAc (Figure 3). The reactions were halted by adding 5 μL of 0.1 M DTPA. The reaction yields were determined by the ITLC method described previously (Ma et al., *Nucl. Med. Biol.*, 29, 91-105 (2002)). The ~~^{177}Lu-DOTA-Herceptin™~~ ^{177}Lu-DOTA-HERCEPTIN conjugates were purified through a 10-DG desalting column (Bio-Rad, Hercules, CA) eluted using PBS and the antibody peaks were collected. Purity of the ^{177}Lu radiolabeled ~~DOTA-Herceptin™~~ DOTA-HERCEPTIN radiolabeled immunoconjugates was determined using ITLC and/or size exclusion HPLC (SE-HPLC).

Please replace paragraph [0119] with the following:

[0119] Radio-iodination of ~~Herceptin™~~ HERCEPTIN with Na ^{125}I was performed as described using the Iodogen method (Fraker et al., *Biochem. Biophys. Res. Commun.*, 80,

849-857 (1978)). The product was purified using a desalting column (PD-10; Amersham Biosciences, Piscataway, NJ).

Please replace paragraph [0121] with the following:

[0121] The immunoreactivity of the RIC was assessed in a live-cell radioimmunoassay (RIA) as detailed elsewhere (Garmestani et al., *Nucl. Med. Biol.*, 29, 599-606 (2002)). HER2 positive cells (N87) were harvested, pelleted at 1,000 x g (Allegra 6KR; Beckman Coulter, Palo Alto, CA) and resuspended in PBS (pH 7.2) containing 1% BSA and were added to 12 x 75 mM polypropylene tubes (1 x 10^6 cells in 100 μL). Serial dilutions of the radiolabeled ~~Herceptin™~~ HERCEPTIN preparations (about 200,000 cpm -12,500 cpm in 50 μL) were then added in duplicate and gently shaken. Following an overnight incubation at 4 °C, the cells were washed once with 4 mL of 1% BSA in PBS and pelleted at 1,000 x g for 5 min, and the supernatant was decanted. The pelleted cells were then counted in a γ-scintillation counter (Packard), and the percent binding was calculated for each dilution. The values presented in Table 1 are an average of the serial dilutions. To confirm the specific reactivity of the RIC, cells were incubated with about 200,000 cpm of the RIC along with an excess (10 μg) of unlabeled ~~Herceptin™~~ HERCEPTIN.

Please replace paragraph [0123] with the following:

[0123] An *in vitro* serum stability study was performed with all four of the above radioimmunoconjugates prepared in Example 16 with the measurements being determined by ITLC and size exclusion high performance liquid chromatography (SE-HPLC) methods over two months. The purified ~~^{177}Lu-DOTA-Herceptin™~~ ^{177}Lu-DOTA-HERCEPTIN conjugates (2 mL each) were mixed with 2 mL human serum (Gemini Bioproducts, Woodland, CA). The mixtures were maintained in a 5% CO_2 incubator at 37 °C. At different time points, 50 μL aliquots were taken, mixed with 5 μL of 0.1 M DTPA, and incubated at 37 °C for 30 min. The percentage of ^{177}Lu associated with the immunoconjugate was analyzed by both ITLC (Figure 3) and SE-HPLC (Figure 4). The ~~^{177}Lu-DOTA-Herceptin™~~ ^{177}Lu-DOTA-HERCEPTIN conjugate demonstrated superior stability among the four different DOTA immunoconjugates that were investigated. Both of the ^{177}Lu-C-DOTA and the ~~1B4M-DOTA (7)-Herceptin™~~ 1B4M-DOTA (7)-HERCEPTIN conjugates exhibited similar stability. The

~~^{177}Lu-CHX-DOTA (14) Herceptin™~~ ^{177}Lu-CHX-DOTA (**14**)-HERCEPTIN conjugate appeared to be less stable.

Please replace paragraph [0124] with the following:

[0124] This example demonstrates *in vitro* stability of a compound of formula [III] (PIP-DOTA) conjugated to ~~Herceptin™~~ HERCEPTIN and complexed to a radioisotope.

Please replace paragraph [0125] with the following:

[0125] An *in vitro* serum stability study was performed on piperidinyl-substituted ~~DOTA-Herceptin™~~ DOTA-HERCEPTIN conjugates, as prepared in Example 15, that were complexed to ^{205}Bi, ^{153}Gd or ^{86}Y, as prepared in Example 16. The purified PIP-DOTA radioimmunoconjugates (2 mL each) were mixed with 2 mL human serum (Gemini Bioproducts, Woodland, CA). The mixtures were maintained in a 5% CO_2 incubator at 37 °C. At different time points, 35 μL (^{205}Bi) or 80 μL (^{153}Gd and ^{86}Y) aliquots were taken, mixed with 5 μL of 0.1 M DTPA, and incubated at 37 °C for 30 min. The percentage of ^{205}Bi, ^{153}Gd or ^{86}Y associated with the PIP-DOTA immunoconjugate was analyzed by SE-HPLC. The ^{205}Bi and ^{153}Gd conjugates demonstrated superior stability over time.

Please replace paragraph [0127] with the following:

[0127] The radioimmunoconjugates (RICs) were compared *in vivo* using athymic mice bearing human colon adenocarcinoma xenografts. Female athymic mice (nu/nu), obtained from Charles River Laboratories (Wilmington, MA) at 4-6 weeks of age, were injected subcutaneously on the flank with 2 x 10^6 LS-174T cells in 0.2 mL of RPMI-1640. At approximately 10-14 days, when the tumors measured between 0.4-0.6 cm in diameter, the mice received the ^{177}Lu-labeled ~~Herceptin™~~ HERCEPTIN . The mice were injected with each RIC (about 5 μCi of each) intravenously (i.v.) *via* the tail vein. Mice (n = 5) were sacrificed by exsanguination at 24, 48, 72, 96 and 168 h.

Please replace the title of Table 2 with the following:

Table 2. Biodistribution of ~~Herceptin™~~ HERCEPTIN radiolabeled with ^{177}Lu using bifunctional chelates after intravenous injection: Percent Injected dose/gram

Please replace paragraph [0131] with the following:

[0131] The CHX-DOTA (**14**) RIC resulted in the highest values throughout the study. At 24 h, the femur %ID/g is 3.52 ± 0.67, which then peaks at 96 h at 4.04 ± 0.88. In contrast, the RIC consisting of the PA-DOTA ligand yielded the lowest femur %ID/g with 1.98 ± 0.17, which declined to 0.97 ± 0.17 and 1.04 ± 0.16 at 96 and 168 h, respectively. The ^{177}Lu-C-DOTA and 1B4M-DOTA (**7**) ~~Herceptin™~~ HERCEPTIN conjugates were not appreciably different from each other, and both were intermediate in the femur %ID/g as compared to the CHX- and PA-DOTA RIC. Differences among the ^{177}Lu-labeled RIC were also evident in the %ID/g calculated for the tumor xenografts and the other normal tissues that were collected (Table 2).

Please replace paragraph [0132] with the following:

[0132] The greatest uptake in tumor by a RIC was observed with the ^{177}Lu-1B4M-DOTA (**7**) ~~Herceptin~~ HERCEPTIN. At 48 and 72 h the tumor %ID/g was 42.46 ± 12.35 and 39.22 ± 6.50, respectively. The lowest values, 26.78 ± 3.25 and 24.23 ± 11.96, were obtained with the CHX-DOTA (**14**) RIC at the same time points.

Please replace paragraph [0134] with the following:

[0134] In other normal tissues, the C-DOTA RIC resulted in the highest kidney %ID/g at each of the study time points with the exception of 168 h, at which a value of 2.79 ± 0.37 was obtained with the CHX-DOTA (**14**) RIC. The spleen %ID/g was the greatest with the PA-DOTA RIC from 24-72 h, while higher values were determined at 96 and 168 h with the C-DOTA RIC. The lowest spleen %ID/g values were obtained with ~~^{177}Lu-1B4M-DOTA-Herceptin~~ ^{177}Lu-1B4M-DOTA-HERCEPTIN at 24, 48 and 168 h and with the CHX-DOTA (**14**) RIC at 72 and 96 h.

Please replace the footnote for Table 3 with the following:

[a]Athymic mice bearing s.c.human colon carcinoma (LS-174T) xenografts were co-injected i.v. with approximately 2-5 μCi of ^{177}Lu-labeled immunoconjugates and ~~^{125}I-Herceptin~~ ^{125}I-HERCEPTIN. The mice (n=5) were sacrificed by exsanguinations as described above. The blood, tumor and major organs were collected and wet-weighed, and the radioactivity was measured. The tissue-to-blood ratios were calculated for each tissue.